Endothelial dysfunction in the outer medullary vasa recta as a key to contrast media-induced nephropathy

William H. Beierwaltes

1Hypertension and Vascular Research Division, Department of Internal Medicine, Henry Ford Hospital, Detroit, Michigan; and 2Department of Physiology, Wayne State University School of Medicine, Detroit, Michigan

The role of the endothelium in the adverse reaction of blood vessels to contrast media imaging agents, and in particular the sensitivity of the kidney, has been a subject of interest dating back to 1964 (2). The renal vasculature seems particularly sensitive to the influence of endothelium-derived nitric oxide vasodilation (7) and its buffering of endogenous vasoconstrictors. Thus the possible interaction between contrast agents and renal vascular resistance has become a subject of intense interest, in particular regarding the possible role of endothelial dysfunction in contrast media-induced nephropathy. Several particular points regarding contrast agent toxicity have been established. First, all contrast media are cytotoxic (5), and virtually all cells may be subject to this cytotoxicity to some extent. This may be compounded by the nature of the specific contrast media, such as its ionic strength, osmolality, or viscosity (4). Contrast media have been reported to induce necrosis and apoptosis in renal tubular cells (3), and disrupt nitric oxide-mediated vasodilation without altering anatomic integrity in systemic and renal cortical endothelia (9). These detrimental interactions may be particularly important in the kidney due to the particularly increased sensitivity of the renal endothelium in maintaining renal perfusion (7) and the fact that the content of the renal tubules and postglomerular juxtedudary capillaries (vasa recta) becomes more concentrated as they descend into the medulla (4), strengthening the potential toxicity of the contrast media. While medullary blood flow accounts for only ~20% of total renal blood flow, perfusion of this anatomic region is critical for the concentrating mechanisms of the kidney, as well as regulated sodium reabsorption and its potential involvement in sodium-induced hypertension.

The outer medullary vasa recta are particularly suited for regulating medullary perfusion as they are simple vessels composed of an endothelial lining surrounded by constrictor pericytes. The deep medullary vasa recta become little more than an endothelial sleeve which is unlikely to regulate perfusion, although it may play a role in endothelium-mediated selective permeability of the deep vessel. Cao et al. (1) have documented that endothelium-derived nitric oxide is a critical vasodilatory regulator of descending vasa recta perfusion, which acts in juxtaposition to the constrictor action of endogenous superoxide. Nitric oxide synthase inhibition reduces (total kidney) renal blood flow some 35%, with coupled decreases in glomerular filtration rate (GFR) and increased renal vascular resistance, and these changes have been shown to be directly linked to the endogenous levels of the renin-angiotensin system (1). Because the medullary vasa recta are in series and downstream from the afferent and efferent resistance vessels, changes in vascular resistance may be even more amplified in the medulla if endothelial integrity is compromised. The importance of this topic is underlined by the disproportionately high number of review articles addressing the subject.

With all of these potential problems pointing to an exaggerated vulnerability of the medullary circulation to compromised endothelial function, in an issue of the American Journal of Physiology-Renal Physiology Sendeski et al. (6) from the Berlin group (which includes some of the major contributors to this field) have provided a series of integrated protocols that demonstrate just how important the outer medullary vasa recta endothelium is in contrast media-induced acute kidney injury. First, they tested the perfusion of both viable human and rat isolated, perfused renal medullary descending vasa recta and found that exposure to contrast media resulted in significant pericyte-mediated vasoconstriction to a luminal diameter smaller than that of a red blood cell. They found that angiotensin-induced constriction was exaggerated after exposure to contrast media, but was diminished by adrenomedullin, which has endothelial-preserving properties. They also report (6) not just endothelial dysfunction but also significant physical damage by contrast media to endothelial integrity. These are coupled with large changes in electrical resistance along with increased myosin light chain kinase phosphorylation, all of which support compromised endothelial integrity, altered barrier permeability, in addition to dysfunction of intrinsic endothelium-mediated vasodilation.

Several things stand out about this important work (6). First, the concentrations of contrast media were similar to what might be expected during a human angiographic procedure, suggesting these results are not some pharmacological artifact. Second, for those skeptical of animal models of human disease, the group found that the human and rat data were essentially identical. Contrast media evoked similar detrimental responses, physical damage, and compromised perfusion in both species. Finally, they report not only that altered endothelium-mediated function is compromised but that this is coupled with the compromised histological appearance of the endothelium. This is contrary to what has been shown in the cortex (9) and explains why the agent-induced pathology may not be readily reversible. There is not just the loss of nitric oxide synthesis but an alteration of anatomic integrity, compromised permeability of the endothelial barrier, and excessive pericyte constriction, all which lead to the compromised function, ischemic damage, and ultimately to kidney injury. The authors focus on only the medullary circulation, as they have previously suggested this is a likely target (4), and while the cortical circulation is no doubt compromised, the greater blood flow, fluid
exchange, and isosmotic nature of the cortex reduce potential damage compared with the medulla.

Beyond describing the character of the changes and pathology of the descending vasa recta in their models, they also use the peptide adrenomedullin (6), which has been reported to buffer the endothelial cell from inflammation by stabilizing endothelial cell barrier function (as reviewed in Ref. 8). They report that adrenomedullin treatment attenuated the contrast media-induced vasoconstriction by about half in both human and rat vasa recta (6). They found that the enhanced angiotensin-induced constriction after contrast media treatment was also diminished by adrenomedullin. This represents a logical yet novel application of adrenomedullin to counteract contrast-induced endothelial damage. Typically, patients are subjected to positive hydration before treatment to reduce the potential toxicity of the contrast agent to the kidney by minimizing concentration and osmotic effects (4). While not a focus of this particular work, it would not be surprising to see additional studies from this group testing the efficacy of adrenomedullin as a preventative treatment to preserve endothelial function during contrast media administration.

Overall, the impact of contrast media-induced endothelial damage in the descending vasa recta is a complex issue, involving an imbalance of the endothelium-derived vasodilator nitric oxide and constrictors such as superoxide and angiotensin, increasing resistance, cytotoxicity, and physical damage to a fragile but essential vascular network, increased ischemia, and altered permeability; all of these impair function and promote acute kidney injury as often seen following these imaging procedures. The study by Sendeski et al. (6) provides some critical insight into the underlying pathophysiological mechanisms and hints at potential future therapeutic approaches to minimize the risk of this all-too-common problem.

GRANTS

W. H. Beierwaltes is supported by National Institutes of Health Grant PPG 5PO1HL090550-03.

REFERENCES


DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS

Author contributions: W.H.B. provided conception and design of research; W.H.B. analyzed data; W.H.B. interpreted results of experiments; W.H.B. drafted manuscript; W.H.B. edited and revised manuscript; W.H.B. approved final version of manuscript.